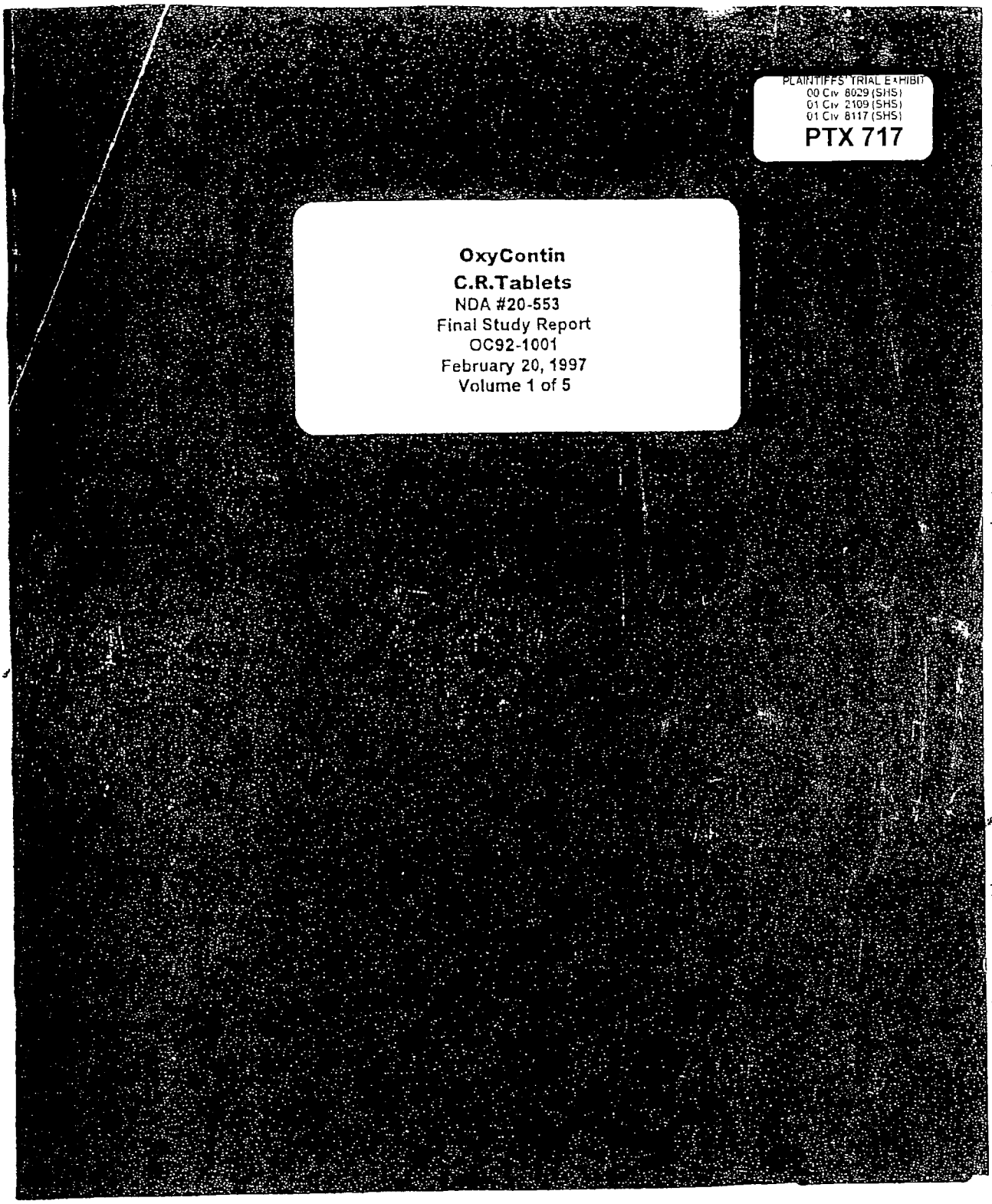
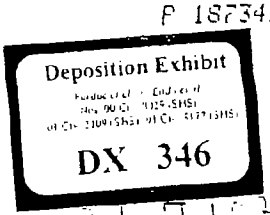


CONFIDENTIAL INFORMATION Purdue v. Boehringer P 187345



bcc: Napp UK
PF Canada

Purdue Pharma L.P.

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IND/NDA

February 20, 1997

SUBMITTED IN DUPLICATE
SUPPLEMENTAL APPLICATION
FINAL POSTMARKETING STUDY REPORT

Curtis Wright, M.D.
Anesthetic/Critical Care & Addiction Drug Products
Office of Drug Evaluation 3
Food and Drug Administration
HFD-170, Document Control Room 9B23
5600 Fishers Lane
Rockville, MD 20857

RE: OXYCONTIN® (oxycodone hydrochloride)
NDA #20-553

Dear Dr. Wright,

Please refer to our New Drug Application, NDA #20-553, for OxyContin® 10, 20 and 40 mg Tablets filed December 28, 1994 (approved December 12, 1995) which included the study protocol only for Study No. OC92-1001. Attached hereto, please find the hard copy Final Study Report.

The primary objectives of this study were to "compare the peak-to-trough fluctuation and the trough variation in steady-state plasma oxycodone and morphine concentrations."

It was concluded that "While CR oxycodone was comparable with CR morphine in efficacy, there were differences in clinical pharmacokinetics that favored CR oxycodone. Similarly, the safety profiles of CR oxycodone and CR morphine were similar, but small differences suggested CR oxycodone may have benefits over CR morphine in individual patients. Overall, this study provides definitive evidence of the clinical equivalence of CR oxycodone and CR morphine in controlling cancer pain."

If you have any questions or require additional information, please contact me at the number below.

Sincerely,

Beth Kennedy
Associate
Drug Regulatory Affairs & Compliance
(203) 854-7289

STUDY REPORT

OxyContin™ Tablets

PROTOCOL NO. OC92-1001

Double-blind, randomized, q12h multiple-dose, parallel-group comparison of the pharmacokinetic and pharmacodynamic profiles of controlled-release oxycodone (OxyContin™) and MS Contin® tablets in patients with chronic cancer-related pain

Investigators:

Barry S. Berman, MD
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Patricia Mucci-LoRusso, DO (#1537)

Michael R. Mullane, MD (#1510)

Winston C.V. Parris, MD, FACPM (#716)

Susan Rabinowe, MD
(previous principal investigator,
William A. Ferri, Jr., MD; #1539)

Peter T. Silberstein, MD (#1488)

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Sponsor

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Analytic Laboratory

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STUDY DATES:

START DATE: June 1, 1994

END DATE: December 27, 1995

REPORT DATE: September 27, 1996

IND. NO. 29,038

FINAL: September 27, 1996

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Vice President

9/27/96
Date

REVISIONS

Revision No.	Revision Date	Revision Approval - P. Goldenheim, M.D.
1		
2		
3		
4		

STUDY REPORT

OxyContin™ Tablets

PROTOCOL NO. OC92-1001

DOUBLE-BLIND, RANDOMIZED, Q12H MULTIPLE-DOSE, PARALLEL-GROUP COMPARISON OF THE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILES OF CONTROLLED-RELEASE OXYCODONE (OXYCONTIN™) AND MS CONTIN® TABLETS IN PATIENTS WITH CHRONIC CANCER-RELATED PAIN

SUMMARY

I. TITLE: Double-blind, randomized, q12h multiple-dose, parallel-group comparison of the pharmacokinetic and pharmacodynamic profiles of controlled-release oxycodone (OxyContin™) and MS Contin® tablets in patients with chronic cancer-related pain

II. INVESTIGATORS

Barry S. Berman, MD (previous principal investigator, Michael S. Roberts, MD; #1557 and 1311)
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Susan Rabinowe, MD (previous principal investigator, William A. Ferri, Jr , MD; #1539)
Peter T. Silberstein, MD (#1488)
Sharon M. Weinstein, MD (#1538)

III. TRIAL DATES: June 1, 1994 to December 27, 1995

IV. OBJECTIVES/STUDY DESIGN: This double-blind, parallel-group study compared the steady-state pharmacokinetic and pharmacodynamic profiles of controlled-release (CR) oxycodone (OxyContin™) and CR morphine (MS Contin®) given q12h in patients with chronic cancer-related pain. The primary objectives were to compare the peak-to-trough fluctuation and the trough variation in steady-state plasma oxycodone and morphine concentrations.

Patients were randomly assigned to treatment with CR oxycodone or CR morphine tablets q12h for 3-12 days. The dose of q12h medication was titrated until pain control was acceptable to the patient and any adverse experiences were tolerable. Rescue medication was allowed. Pharmacokinetic and pharmacodynamic procedures were performed after stable pain control had been maintained for at least 48 hours, at 0 hours and 3 hours after the 8:00 AM dose of study medication. Patients who could not be stabilized within 10 days were discontinued. A total of 60 evaluable patients was planned. Nine sites participated in the study.

Common opioid-related adverse experiences were treated appropriately, and only 9 of 100 patients discontinued for adverse experiences, 3 in the CR oxycodone group and 6 in the CR morphine group. Only one patient had serious adverse experiences, which were related to disease progression. This patient and one additional patient died while hospitalized during the trial. Both of these deaths were caused by disease progression, and were considered by the investigators to be unrelated to the study drug. Two additional patients were hospitalized during the trial for intercurrent diseases and conditions that were not reported as adverse experiences.

Laboratory testing was performed at the end of the trial to help explain any possible aberrant pharmacokinetic-pharmacodynamic results. Many patients had clinically significant abnormalities that were associated with the underlying disease states. No clear patterns of abnormalities that could be attributed to the study drugs were noted.

VII. CONCLUSIONS:

The peak-to-trough fluctuation in steady-state plasma drug concentrations was one-third less with CR oxycodone than with CR morphine. In addition, one-half of the variation in plasma oxycodone concentrations could be attributed to differences in oxycodone dose, while only one-tenth of the variation in plasma morphine concentrations could be attributed to differences in morphine dose CR oxycodone provides more consistent and predictable therapeutic opioid concentrations than CR morphine. There was no difference in the relative variation in trough plasma drug concentrations with CR oxycodone compared with CR morphine.

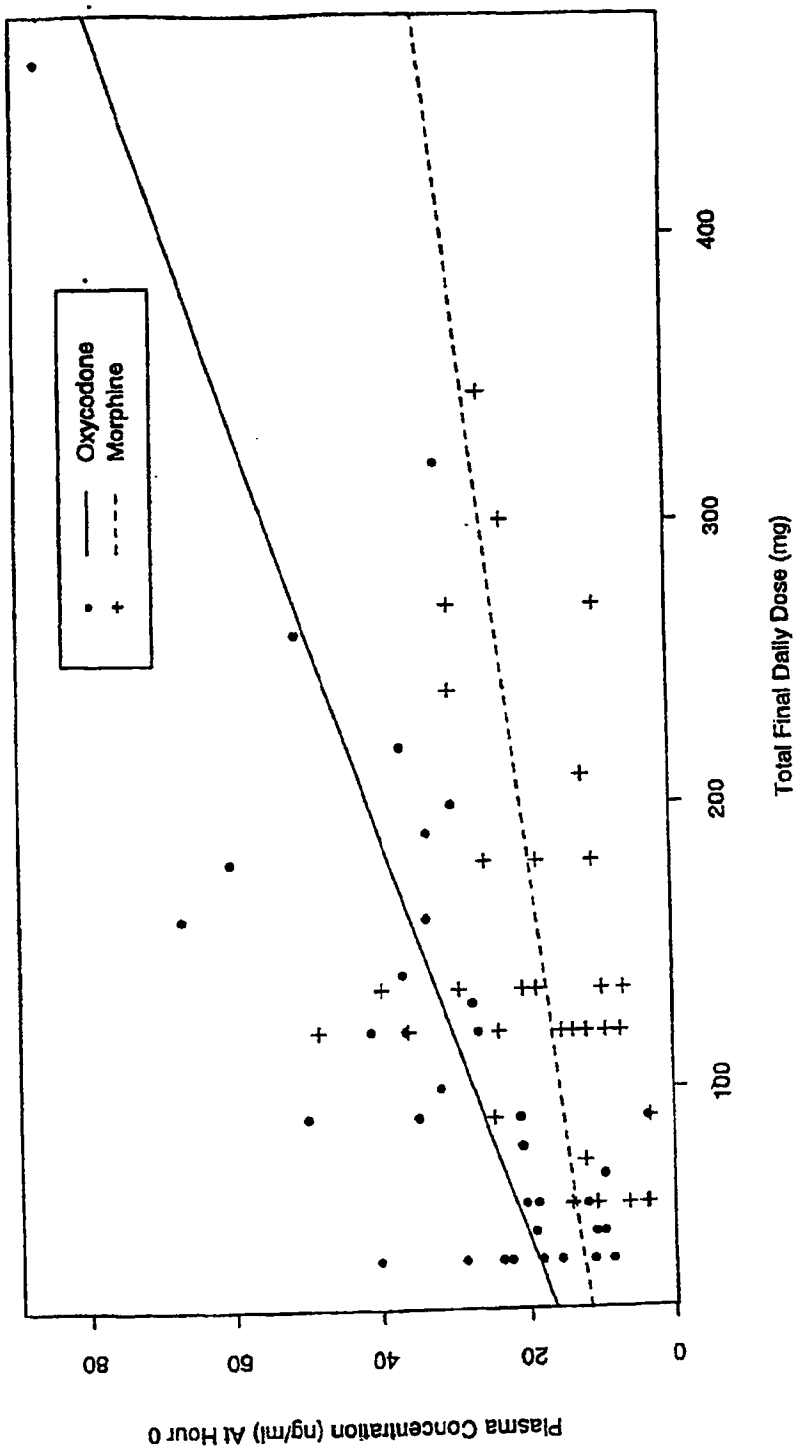
This study did not show an association between laboratory measures of hepatic (AST/SGOT, ALT/SGPT, and bilirubin) and renal (BUN and creatinine) function and the plasma concentration profiles of oxycodone and its metabolites, noroxycodone and oxymorphone. In comparison, plasma concentrations of the active metabolite of morphine, morphine-6-glucuronide, increased with increasing BUN and creatinine levels This provides further evidence of the consistency of plasma oxycodone concentrations in this patient population.

CR oxycodone was as effective as CR morphine in relieving pain in cancer patients. The median time to achieve stable pain control was two days with both treatments, and the number of dose adjustments required and rescue medication use were similar for both drugs. Rescue use was quite infrequent (an average of one dose per day). Pain intensity was "slight," acceptability of therapy was "good," and quality of life was similar with both treatments. The safety profiles of CR oxycodone and CR morphine were similar, and were typical of opioid analgesics. However, there were small differences that favored CR oxycodone. No patients treated with CR oxycodone experienced hallucinations, compared with two patients treated with CR morphine. Also, patients' ratings of itching and observers' ratings of scratching were lower in the CR oxycodone group than in the CR morphine group. There was a significantly more positive relationship between plasma oxycodone concentrations and analgesia compared with plasma morphine concentrations and

analgesia. However, there were no strong or predictive correlations between plasma opioid concentrations and pain intensity, MSDEQ scores, or scores for drowsiness or nausea.

While CR oxycodone was comparable with CR morphine in efficacy, there were differences in clinical pharmacokinetics that favored CR oxycodone. Similarly, the safety profiles of CR oxycodone and CR morphine were similar, but small differences suggested CR oxycodone may have benefits over CR morphine in individual patients. Overall, this study provides definitive evidence of the clinical equivalence of CR oxycodone and CR morphine in controlling cancer pain.

PROTOCOL NO. OC92-1001
Figure 1
PLASMA CONCENTRATION AT HOUR 0 AND DAILY DOSE
Population: Patients Valid for Cmax/Cmin Analysis



3.0 FULL STUDY REPORT

3.1 Introduction

Oxycodone hydrochloride is an opioid analgesic with pharmacological activity similar to that of morphine. In the US, oxycodone has most often been used in a fixed-dose combination with a nonopioid analgesic. Because the dose of the combination product is limited by side effects associated with the nonopioid component, these products are not usually used for the treatment of severe pain. Oxycodone itself has no analgesic ceiling. Single-entity oxycodone has been shown to be safe and effective at much higher doses than oxycodone in fixed combination,[1] and is clinically effective in the treatment of moderate to severe postsurgical pain[2-4] and severe cancer pain.[5]

Controlled-release (CR) oxycodone hydrochloride (OxyContin™) tablets have recently been approved in the U.S., Canada, Denmark, and Finland for the treatment of moderate to severe pain. CR oxycodone is formulated to be taken every 12 hours (q12h), and provides the advantages of a single-entity oxycodone product with the convenience of q12h dosing. Until recently in the U.S., morphine sulfate was the only opioid analgesic available in an oral CR formulation (MS Contin® tablets). This double-blind, parallel-group study compared the steady-state pharmacokinetic and pharmacodynamic profiles of CR oxycodone and CR morphine given q12h in patients with chronic cancer-related pain.

3.2 Study objectives

The primary objectives of this study were the following:

- To test the hypothesis that no difference exists between the two treatments in the peak-to-trough fluctuation in steady-state plasma oxycodone or morphine concentrations.
- To test the hypothesis that no difference exists between the two treatments in the relative variation in steady-state trough plasma oxycodone or morphine concentrations.

The following were additional objectives of the study:

- To compare the steady-state plasma concentration-pain intensity relationship between the two treatment groups.
- To compare the steady-state plasma concentration-side effect relationship between the two treatment groups.
- To compare the steady-state plasma concentration-total daily dose relationship between the two treatment groups
- To evaluate the steady-state plasma concentration-total daily dose relationship between the two treatment groups by patient characteristics.

- To compare time to achieve a stable regimen between the two treatment groups.
- To compare acceptability of analgesic treatment between the two treatment groups.
- To compare quality of life between the two treatment groups using the Functional Assessment of Cancer Therapy-General (FACT-G) scale.[5]

3.3 Investigational plan

3.3.1 Overall design and plan of the study

In this double-blind, parallel-group, multicenter study, patients with chronic cancer-related pain were randomly assigned to treatment with CR oxycodone or CR morphine q12h for 3-12 days. The dose of the q12h medication was titrated, if necessary, until stable pain control was maintained for at least 48 hours. Rescue medication for breakthrough pain was allowed in both groups: immediate-release (IR) oxycodone in the CR oxycodone group and IR morphine (MSIR®) in the CR morphine group. Pain control was considered stable when, over a 48-hour period, the q12h dose was unchanged, ≤ 2 rescue doses were taken in each 24-hour period, the dosing regimen for any nonopioid analgesics or adjuvant medications with analgesic properties were unchanged, and the patient reported that pain control was acceptable and any adverse experiences were tolerable. Pharmacokinetic and pharmacodynamic procedures were performed after stable pain control had been maintained for at least 48 hours Patients who could not be stabilized within 10 days were discontinued. Eighty evaluable patients were planned.

3.3.2 Study rationale/discussion of choice of design

CR oxycodone and CR morphine are controlled-release formulations of opioid analgesics approved for the relief of moderate to severe pain. This double-blind study compared the steady-state pharmacokinetic and pharmacodynamic profiles of these two products in patients with chronic cancer-related pain. On average, steady-state is attained in a day with both drugs. To ensure steady-state conditions, pharmacokinetic and pharmacodynamic assessments were made after stable pain control was maintained for at least 48 hours. The time to maximum plasma concentration (T_{max}) is approximately 3 hours for both drugs, and blood samples for peak plasma concentrations were taken at 3 hours after dosing. Samples for trough concentrations were taken just prior to dosing.

The "double-dummy" technique was used to blind the q12h study medications Patients took an equal number of active and placebo tablets for each q12h dose. In order to use this technique with the tablet strengths available at the time of this study, patients randomized to receive CR morphine received a milligram dose that was 1.5 times that of the CR oxycodone dose. However, the relative potency of oral CR oxycodone to oral CR morphine was determined to be 2:1,[7] and the recommended conversion ratio is 1 mg of oral oxycodone for every 2 mg of oral morphine.[8,9]

Rescue medications were blinded by encapsulating the appropriate number of IR tablets so that the IR oxycodone and IR morphine appeared identical.

3.3.3 Study population

Patients who required treatment with opioid analgesics for chronic, cancer-related pain were enrolled according to the following inclusion and exclusion criteria.

3.3.3.1 Inclusion criteria

- Male or female patient 18 years of age or older.
- Cancer-related pain for which around-the-clock treatment with an oral, controlled-release opioid is appropriate.
- Required, or was expected to require, total daily oral oxycodone doses between 30 and 340 mg. Patients on maximally labeled doses of nonopioids were eligible if pain was not controlled and the investigator deemed that the patient required minimum opioid dose per protocol.
- If outpatient, must have been able to be contacted by telephone.
- Able to read, understand, and sign written informed consent.
- Rational, reasonably responsive, capable of subjective evaluation, and expected to be able to follow the procedures of this study.
- If coexisting disease(s) or condition(s) were present, the disease states and related therapies must have been stable for at least one week prior to entry.

3.3.3.2 Exclusion criteria

- History of sensitivity to or a medical contraindication for the use of oral oxycodone or oral morphine
- Contraindication for opioid therapy, such as paralytic ileus or severe pulmonary disease (listed in Appendices II and III of the protocol, included in Appendix II of this report)
- Receiving an opioid analgesic that could not be discontinued at study entry.
- Unable to take oral medication.
- Severely compromised organ function (such as lungs, gastrointestinal tract, kidney, liver, or CNS) that, in the judgment of the investigator, may adversely affect safety or obscure efficacy.
- Expected to have surgery or other procedure(s) that would prevent completion of the 3-12 day study.
- Female patient who was pregnant or nursing.
- Female patient of childbearing potential who did not agree to follow a medically recognized method of pregnancy protection.
- Participation in another IND investigational drug or device study.
- History of severe lactose intolerance

3.3.4 Treatment allocation/randomization

Patients were randomly assigned to one of two treatment groups, CR oxycodone or CR morphine. The randomization code was generated by the Biostatistics and Clinical Data Management Department of The Purdue Frederick Company according to established standard operating procedures.

3.3.5 Study drugs

3.3.5.1 Test materials

- OxyContin™ (oxycodone hydrochloride controlled-release) Tablets, 20 mg active and placebo (pink tablet)
- MS Contin® (morphine sulfate controlled-release) Tablets, 30 mg active and placebo (purple tablet)
- Immediate-release oxycodone, 10 mg capsules (two 5-mg tablets in green capsule filled with lactose)
- MSIR® (IR morphine sulfate), 15 mg capsules (one 15-mg tablet in green capsule filled with lactose)

3.3.5.2 Dosage/administration/route/exposure/dosage range

Controlled-release opioids were taken orally q12h at 8:00 AM and 8:00 PM (± 1 hour). Study drugs were packaged to accommodate 10 dose levels. Oxycodone was packaged to permit administration of a minimum dose of 20 mg q12h to a maximum dose of 200 mg q12h. Morphine was packaged to permit administration of a minimum dose of 30 mg q12h to a maximum dose of 300 mg q12h. A total of four rescue doses per day were included in the package for oxycodone or morphine.

Patients discontinued use of any opioid analgesics at least 4 hours before the first dose of study medication, based on the duration of action of the prestudy opioid. Patients receiving transdermal fentanyl discontinued the patch at least 12 hours before the first dose of study medication.

3.3.5.2.1 Controlled-release study medication

The initial daily dose of study medication was calculated by converting the patient's prestudy daily opioid dose to oral oxycodone using conversion factors specified in the protocol (Appendix V of the protocol, included in Appendix II of this report). The results from each opioid were added to obtain the total daily oral oxycodone dose. Patients were eligible if the total daily dose was between 30 and 340 mg (corresponding to dose levels 1-8). The q12h oral oxycodone equivalent dose was calculated by dividing the daily dose by 2 and rounding to the nearest multiple of 20 mg. The dose of CR morphine (1.5x) was fixed by packaging to the oxycodone dose. The patient was then randomized. The initial dose could be increased or decreased by one dose level at the discretion of the investigator. The reason for not using the calculated dose level, e.g., severe pain or adverse experience, was documented.

Patients were instructed to take the appropriate number of CR oxycodone tablets and an identical number of CR morphine tablets q12h, with the knowledge that one of the medications was a placebo. They took the q12h study medication at 8:00 AM and 8:00 PM (± 1 hour) daily. Tablets were swallowed whole; they could not be crushed, chewed, or cut.

Upward dose titration could be performed when either or both of the following occurred:

- The patient reported that pain control was unacceptable (usually pain intensity greater than "slight") over two consecutive categorical pain evaluations, or that breakthrough pain was occurring regularly toward the end of the q12h dosing interval.
- More than two doses of rescue medication were taken over a 24-hour period.

The dose was usually increased by one dose level, and could not be increased more frequently than once every 24 hours.

Downward dose titration was considered when unacceptable opioid-related adverse effects were noted. In addition, adverse effects were treated as outlined in section 3.3.6. When dose reduction was required, the usual decrease was one dose level. Dose reduction continued until adverse effects were absent or tolerable.

If the dose was not adjusted as specified above, the reason was documented.

3.3.5.2.2 Rescue medication

Most doses of rescue medication were approximately 1/4 to 1/3 of the q12h scheduled dose. The rescue medication was blinded by encapsulation so that the dose of one capsule (10 mg oxycodone or 15 mg morphine) equaled 1/2 the dose of one active tablet. The number of capsules required for each rescue dose was specified for the 10 dose levels (Appendix IV of the protocol, included in Appendix II of this report). Rescue medication could be taken as needed, but not more frequently than once every 2-4 hours. To control incident pain, rescue medication could be given 1 hour before the activity causing pain. Capsules were swallowed whole without being opened.

3.3.5.3 Blinding/packaging

The controlled-release opioids were blinded using a "double-dummy" technique, which required that patients take an equal number of active and placebo tablets for each q12h dose. Patients in the CR oxycodone group received placebo tablets matched to CR morphine, and those in the CR morphine group received placebo tablets matched to CR oxycodone. The IR opioids used for rescue medication were blinded by encapsulation.

Study medication was packaged on daily blister cards that contained the q12h controlled-release opioid, both active and placebo, and the IR rescue opioid. A total of four rescue doses per day was contained on each blister card. The rescue dose was determined from the q12h dose, and could range from 1-5 capsules per dose. The blister cards were prepackaged according to a randomization code generated by the Biostatistics and Clinical Data Management Department of The Purdue Frederick Company. Each patient package contained 12 daily blister cards. The blister cards were perforated in several sections so that medications required for higher dosages could be removed prior to dispensing study medication to patients requiring lower dosages. Alternatively, labels could be affixed over the doses that were not to be taken by a patient.

Plasma samples were analyzed for oxycodone, oxymorphone, and noroxycodone concentrations using gas chromatography/mass spectrometry (GC/MS) technology. The minimal quantifiable level for all analytes was 0.2 ng/mL.

Plasma samples were analyzed for intact morphine and morphine-6-glucuronide using a validated high performance liquid chromatographic (HPLC) method. The minimal quantifiable level was 1.0 ng/mL for morphine and 5.0 ng/mL for morphine-6-glucuronide.

3.3.9 Removal of patients from study

The investigator could discontinue a patient from the study for any reason, including the following:

- Adverse experience: unacceptable or untreatable adverse experience,
- Ineffective treatment: ineffective pain control or inability to achieve a stable dose within 10 days,
- Illness not due to drug: development or worsening of a disease or condition that necessitated premature discontinuation,
- Death,
- Lost to follow-up: failure to cooperate or to return for the final visit,
- Protocol violation: failure to comply with the protocol requirements or development of clinical findings that no longer met the inclusion and exclusion criteria.

Patients could withdraw their consent to participate in the study at any time.

3.4 Study variables

3.4.1 Pharmacokinetic variables

- Plasma drug concentrations at trough (C_{min}) and peak (C_{max}) were measured from blood samples taken at 0 hours and 3 hours after dosing, respectively.

- The scaled difference between the concentration values was defined as

$$C_{max} - C_{min}/\text{mean } C_t$$

where mean C_t is the average of the concentration values. This was used to measure the peak-to-trough fluctuation.

- The relative variability of C_{max}, C_{min}, and the scaled difference (expressed as the coefficient of variation [CV = standard deviation/mean]) was calculated for each treatment.

3.4.2 Pharmacodynamic variables

The following pharmacodynamic assessments made at the two blood sampling times were analyzed:

(constipation, dizziness, dry mouth, nausea, pruritus, somnolence, and vomiting) divided by total days exposure to study drug, was calculated for each treatment group. This analysis was done for the intent-to-treat and pharmacokinetic-pharmacodynamic populations.

Three statistical analyses planned in the protocol were not performed because they were not thought to be necessary. The between-group difference in the total number of patients reporting adverse experiences was to have been tested with Fisher's exact test and CMH. A logistic regression analysis of the number of patients with ("yes") or without ("no") adverse experiences was to have been done with treatment and plasma concentration as explanatory variables. Treatment side effect odds ratio and its 95% confidence interval was to have been calculated.

3.6.3.7.2 Clinical laboratory evaluations

Abnormal laboratory values were tabulated by patient and treatment. The abnormalities were reviewed by the patient's physician and the data listing of individual results was reviewed by the sponsor's medical officer (Data Listing 24).

3.7 Results

3.7.1 Disposition of patients entered/administrative reporting

3.7.1.1 Patients

A total of 101 patients were enrolled in the study (Table 1A). One patient (#716-205) did not take any study medication (patient refused to participate) and was not included in any analyses Evaluability groups are described in section 3.6.2. The intent-to-treat population included 100 patients, 48 in the CR oxycodone group and 52 in the CR morphine group (Table 1B). Of these patients, 82 were titrated to stable pain control, 40 in the CR oxycodone group and 42 in the CR morphine group. Two patients (#1539-159 in the CR oxycodone group and #1537-133 in the CR morphine group) completed the study, including pharmacokinetic-pharmacodynamic assessments, but did not reach stable pain control as defined in the protocol (see section 3.3.1). Patient #1539-159 was included in the pharmacokinetic-pharmacodynamic and C_{max}/C_{min} populations (Data Listing 2). Patient #1537-133 was excluded from the pharmacokinetic-pharmacodynamic population because a change was made in the dose of a nonopioid analgesic before the assessments were made.

Sixteen patients (seven in the CR oxycodone group and nine in the CR morphine group) who did not reach stable pain control within the 10 days required by the protocol were discontinued from the study for the following reasons:

- adverse experience--8 patients,
- ineffective treatment--2 patients,
- intercurrent illness--3 patients,
- protocol violation--1 patient, and
- other reason--2 patients

Four patients (two in each group) reached stable pain control but discontinued the trial. One patient each discontinued for adverse experience, intercurrent illness, protocol violation, and other reason.

3.7.1.2 Study regimen

This was a double-blind, parallel-group study in which patients were randomly assigned to treatment with CR oxycodone or CR morphine for 3-12 days. The study medication was titrated until pain control was acceptable to the patient and any adverse experiences were tolerable. Rescue medication was allowed. Pharmacokinetic and pharmacodynamic procedures were performed after stable pain control had been maintained for at least 48 hours. Patients who could not be stabilized within 10 days were discontinued.

Patient evaluability was determined before the study blind was broken. The definitions of the evaluability groups were recorded in a memorandum dated April 17, 1996. The study blind was broken on April 23, 1996.

3.7.1.3 Protocol violations/evaluability of patients

Protocol violations were noted in 12 patients in the CR oxycodone group and 11 patients in the CR morphine group. Most of these violations were related to pharmacokinetic-pharmacodynamic assessments. Two patients were considered discontinued because of protocol violations, although one of these patients, #1311-146, completed all study procedures and the data were allowed in the analyses. The second discontinued patient, #1537-135, did not complete the study procedures. Of the patients who had pharmacokinetic-pharmacodynamic assessments, three were excluded from the pharmacokinetic-pharmacodynamic analysis and 16 were excluded from the C_{max}/C_{min} analysis because of protocol violations. The effect of protocol violations on patient evaluability is noted in footnotes to the following tables.

The following general protocol violations were noted; these patients were included in the intent-to-treat analyses:

	CR oxycodone	CR morphine
Did not meet criteria for stable pain control	1539-159[4]	1537-133[2,3] 1538-177[3]
Received prohibited opioid analgesic	1537-136[4] 1538-176[2,3]	1537-135[1]
Recording of rescue medication inaccurate		1538-177[3]
Prestudy opioid taken < 4 h from first dose of study medication	1557-152[4]	

[1]Patient considered discontinued because of protocol violation
[2]Excluded from PK/PD analysis
[3]Excluded from C_{max}/C_{min} analysis
[4]Allowed in PK/PD and C_{max}/C_{min} analysis

Kaplan-Meier estimates of time to achieve a stable regimen (Intent-to-treat population)

	CR oxycodone	CR morphine
N	48	52
Mean (days)	2.8	2.6
SE	0.5	0.4
Median (days)	2	2

(Cross-reference: Table 13; Data Listing 13; Appendix IV)

3.7.5.2 Secondary efficacy results

3.7.5.2.1 Titration to a stable dosing regimen

The percentage of patients titrated to a stable regimen was 83% with CR oxycodone and 81% with CR morphine (Table 1B; Figure 4). There was no statistically significant difference between groups (p=0.799; Fisher's exact test). Of the 16 patients who did not reach stable pain control within the 10 days required by the protocol, 8 discontinued for adverse experiences, 2 for ineffective treatment, 3 for intercurrent illness, 1 for protocol violation, and 2 for other reasons

3.7.5.2.2 Pain intensity

Each morning and evening, patients rated pain intensity since the last q12h dose on a categorical scale (Tables 14.1A-C and 14.2A-C). As noted in section 3.4.3.2, most of these assessments reflect pain intensity before stable pain control was achieved and thus do not reflect the efficacy of the study drugs when given at a stable dosing regimen. No statistical tests were performed for this variable.

To examine patients' diary assessments of pain intensity once stable pain control was achieved, the morning, evening, and average assessments were analyzed for the 48 hours and 24 hours preceding the pharmacokinetic-pharmacodynamic assessments (Table 15) These assessments were made during the period of stable pain control prior to study completion. Thus, pain scores made during the 48 hours preceding the pharmacokinetic-pharmacodynamic assessments reflect the efficacy of the study drugs. Changes from baseline in pain intensity were also examined (Table 15). Baseline assessments (Table 6B) were made just before the first dose of study medication, and reflected intensity at the time of evaluation ("current") and over the past day ("past 24 hours"). The following table summarizes the results for baseline and the average assessments during the last two days of the study. Figure 5 shows mean pain intensity at 8 time points with 95% confidence intervals.

Mean (SE) pain intensity (categorical scale) at baseline and during last 2 days of study (Pharmacokinetic-pharmacodynamic population)

Last 48 h of study		
	CR oxycodone	CR morphine
Current baseline pain	1.9 (0.1)	1.6 (0.1)
Pain in last 48 h of study	1.3 (0.1)	1.0 (0.1)
Change from baseline	-0.7 (0.2)	-0.6 (0.1)
Last 24 h of study		
	CR oxycodone	CR morphine
Baseline pain over last 24 h	2.1 (0.1)	2.1 (0.1)
Pain in last 24 h of study	1.3 (0.1)	1.1 (0.1)
Change from baseline	-0.8 (0.2)	-1.0 (0.2)

(Cross-reference: Tables 6B & 15; Data Listings 6 & 15; Appendix IV)

At baseline, mean pain intensity was near "moderate" in both treatment groups. For the 48-hour and 24-hour periods prior to study completion, mean pain intensity remained near "slight" in both treatment groups. Within each group, pain intensity decreased significantly compared with baseline ($p \leq 0.0048$ for the 48-hour period and $p \leq 0.0002$ for the 24-hour period). There were no statistically significant between-group differences in mean pain intensity or in changes from baseline.

The fluctuation in pain intensity was similar in the intent-to-treat (Table 16A) and pharmacokinetic-pharmacodynamic (Table 16B) populations. The number of changes in pain intensity averaged approximately two in both treatment groups; there were no significant differences between treatments. Most patients in both groups had three or fewer changes in pain intensity throughout the study.

3.7.5.2.3 Rescue medication use

The number of rescue doses taken during the last two days of the study were summarized for the intent-to-treat (Table 17A) and pharmacokinetic-pharmacodynamic (Table 17B) populations. For patients in the intent-to-treat population, this analysis included the last two days on study drug (Day -2 and Day -1). For patients in the pharmacokinetic-pharmacodynamic population, Day -2 was two days before and Day -1 was one day before the pharmacokinetic-pharmacodynamic assessments. No statistically significant between-group differences were found. The mean number of rescue doses on Days -2 and -1 are summarized in the following table:

Mean (SE) number of rescue doses used during last two days of the study

Intent-to-treat population		
	CR oxycodone	CR morphine
Day -2	0.9 (0.1)	0.7 (0.1)
Day -1	1.1 (0.2)	0.9 (0.2)
Pharmacokinetic-pharmacodynamic population		
	CR oxycodone	CR morphine
Day -2	0.8 (0.1)	0.8 (0.1)
Day -1	1.0 (0.2)	0.8 (0.1)

(Cross-reference: Tables 17A & 17B, Data Listing 17; Appendix IV)

The mean amount (mg) of rescue medication used during the period of stable pain control in the pharmacokinetic-pharmacodynamic population was similar in the CR oxycodone and CR morphine groups, as shown in the following table.

Mean rescue dose (mg) (Pharmacokinetic-pharmacodynamic population)

	CR oxycodone	CR morphine
Day -2	13.9	18.0
Day -1	17.4	18.0

3.7.5.2.4 Acceptability of therapy

In the pharmacokinetic-pharmacodynamic population, acceptability of therapy at the final visit was significantly higher than baseline ($p \leq 0.0061$) in both treatment groups. Mean acceptability increased from 3.1 to 4.0 in the CR oxycodone group and from 3.3 to 3.9 in the CR morphine group (Table 18B; Figure 6.2). There were no statistically significant differences between treatments in acceptability scores or changes from baseline. At the final visit, 74% of the patients in the CR oxycodone group and 77% in the CR morphine group rated acceptability as good or excellent.

In the intent-to-treat population, mean acceptability scores at the final visit and changes from baseline were slightly lower than in the pharmacokinetic-pharmacodynamic population (Table 18A; Figure 6.1). However, mean acceptability scores at the final visit were significantly higher than baseline ($p \leq 0.0296$) in both treatment groups. There were no statistically significant between-group differences. At the final visit, 71% of the patients in the CR oxycodone group and 70% in the CR morphine group rated acceptability as good or excellent.

3.7.5.2.5 Quality of life

Quality of life was assessed using the FACT-G questionnaire,[6] which is analyzed so that higher scores indicate a better quality of life.[14] The highest possible total and subscale scores are:

- Total, 112
- Physical, 28
- Social/family, 28
- Relationship with doctor, 8
- Emotional, 20
- Functional, 28.

FACT-G subscale and total scores and changes from baseline were summarized for the intent-to-treat population (Table 7). Differences between treatment groups for scores at the final visit and changes from baseline were tested using ANOVA. At the final visit, the mean total score in the CR oxycodone group was 77 compared with 72 in the CR morphine group; this difference was not statistically significant. Only one subscale score showed a statistically significant difference between treatments: emotional score was 16 in the CR oxycodone group compared with 15 in the CR morphine group (p=0.0369). Although statistically significant, these scores are virtually identical and do not represent a clinically significant difference. There were no statistically significant differences in change from baseline for any subscale scores nor for total score. Quality of life was similar in patients receiving CR oxycodone compared with those receiving CR morphine.

3.7.5.2.6 Study medication dosing

The median number of dose adjustments made before stable pain control was attained was 0 in both the CR oxycodone and CR morphine groups (Table 19). No dose adjustments were required by 26 of 39 patients (67%) in the CR oxycodone group and 29 of 40 patients (73%) in the CR morphine group. There was no statistically significant difference between groups for the number of dose adjustments. Only three patients (CR oxycodone) required more than three dose adjustments.

The mean daily dose on the first day that pain control was judged to be stable was 101 mg in the CR oxycodone group and 140 mg in the CR morphine group (Table 5.2A). In both treatment groups, mean doses were similar in men and women (Tables 5.2B and C).

Initial and final daily doses were summarized for patients in the intent-to-treat (Tables 5.1.1A-C) and pharmacokinetic-pharmacodynamic (Tables 5.1.2A-C) populations. For the intent-to-treat population, the final dose was the dose taken on the last day of the study. For the pharmacokinetic-pharmacodynamic population, the final dose was the dose taken on the day before pharmacokinetic-pharmacodynamic assessments. These results are summarized in the following table:

Mean (SE) initial and final daily doses (mg) of q12h study medication

Intent-to-treat population		
	CR oxycodone	CR morphine
Initial	63 (6)	114 (10)
Final	103 (11)	142 (13)
Pharmacokinetic-pharmacodynamic population		
	CR oxycodone	CR morphine
Initial	61 (5)	120 (10)
Final	103 (12)	147 (11)

(Cross-reference: Tables 5.1.1A-C and 5.1.2A-C; Data Listing 5.1)

The mean final dose in the pharmacokinetic-pharmacodynamic population differs from the mean daily dose on the first day of stable pain control because some patients reached stability with the evening dose, and the daily dose was calculated using the morning and evening dose for that day even if the morning dose differed from the "stable" dose. In addition, not all patients were available for the final assessments at 48 hours after first reaching stable pain control. Several patients' pain became unstable during this waiting period and the dose was titrated to a different level to achieve stable pain control again.

For each treatment, initial and final doses were similar in both populations, and final doses were higher than initial doses. In the pharmacokinetic-pharmacodynamic population, mean final doses were similar in men and women for both treatments. In the intent-to-treat population, the final dose of CR oxycodone was similar in men and women, while the final dose of CR morphine was approximately 30 mg higher in women than in men.

In the pharmacokinetic-pharmacodynamic population, the ratio of the final daily dose in the CR morphine group to the final daily dose in the CR oxycodone group was 1.4 for q12h study medication and total medication (q12h plus rescue) (Table 5.3). The 95% confidence intervals for these ratios were 1.1 to 1.9 for q12h study medication and 1.0 to 1.9 for total medication. Ratios and 95% confidence intervals were similar in men and women in both treatment groups. This ratio of 1.5 was planned for each dose level in order to blind the study by the double-dummy technique using tablet strengths available at the time of the study CR oxycodone 20 mg tablets and CR morphine 30 mg tablets were used For each q12h dose, patients took an equal number of active CR opioid tablets and placebo tablets matched to the alternative CR opioid.

3.7.5.2.7 Compliance

For the intent-to-treat population (N=100), dosing and drug accountability records were used to estimate compliance. For the CR oxycodone group, 40 out of 48 (83.3%) patients were 100% compliant. Four patients had missing data. For the CR morphine group, 43 out of 52 (82.7%) patients were 100% compliant. Five patients had missing data. Details of

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TABLE 5.1.1A

SUMMARY OF TITRATION

Population: Patients Valid for Intent-to-Treat

	CR Oxycodone		CR Morphine		Total	
	N	%	N	%	N	%
Total Enrollment	48	(100.0)	52	(100.0)	100	(100.0)
Initial Daily Dose (CR Oxycodone / CR Morphine)						
40 / 60	32	66.7	25	48.1	57	57.0
80 / 120	8	16.7	14	26.9	22	22.0
120 / 180	7	14.6	9	17.3	16	16.0
160 / 240	0	0.0	2	3.8	2	2.0
200 / 300	1	2.1	2	3.8	3	3.0
N	48		52		100	
Mean	63.3		114.2		87.5	
Std. Error	6.3		9.5		5.6	
Min	40		60		50	
Median	40		120		50	
Max	280		360		350	
Final Daily Dose (CR Oxycodone / CR Morphine)						
40 / 60	18	37.5	17	32.7	35	35.0
80 / 120	10	20.8	17	32.7	27	27.0
120 / 180	9	18.8	8	15.4	17	17.0
160 / 240	6	12.5	7	13.5	13	13.0
200 / 300	3	6.3	2	3.8	5	5.0
320 / 480	1	2.1	0	0.0	1	1.0
360 / 540	1	2.1	1	1.9	2	2.0
N	48		52		100	
Mean	102.5		141.9		123.0	
Std. Error	10.8		13.2		8.6	
Min	40		60		50	
Median	80		120		100	
Max	360		600		500	

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CROSS REFERENCES:
Data Listing: 5.1